General

Guideline Title

Management of patients with recurrence of diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline.

Bibliographic Source(s)

Nahed BV, Redjal N, Brat DJ, Chi AS, Oh K, Batchelor TT, Ryken TC, Kalkanis SN, Olson JJ. Management of patients with recurrence of diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2015 Dec;125(3):609-30. [56 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The rating schemes used for the strength of the evidence (Class I-III) and the levels of recommendations (Level I-III) are defined at the end of the "Major Recommendations" field.

Target Population

These recommendations apply to adult patients with recurrent low grade glioma with initial pathologic diagnosis of a World Health Organization (WHO) grade II infiltrative glioma (oligodendroglioma, astrocytoma, or oligo-astrocytoma).

Pathology at Recurrence

Question

Do pathologic and molecular characteristics predict outcome/malignant transformation at recurrence?

Recommendations

Isocitrate Dehydrogenase (IDH) Status and Recurrence

Level III. IDH mutation status should be determined as low grade gliomas with IDH mutations have a shortened time to recurrence. It is unclear whether knowledge of IDH mutation status provides benefit in predicting time to progression or overall survival.

TP53 Status and Recurrence

Level III. mutations occur early in low grade glioma pathogenesis, remain stable, and are not recommended as a marker of predisposition to malignant transformation at recurrence or other measures of prognosis.

Methylguanine Methyltransferase (MGMT) Status and Recurrence

Level III. Assessment of MGMT status is recommended as an adjunct to assessing prognosis as low grade gliomas with MGMT promoter methylation are associated with shorter progression-free survival (PFS) (in the absence of temozolomide [TMZ]) and longer post-recurrence survival (in the presence of TMZ), ultimately producing similar overall survival to low grade gliomas without MGMT methylation. The available retrospective reports are conflicting and comparisons between reports are limited.

CDK2NA Status and Recurrence

Level III. Assessment of CDK2NA status is recommended when possible as the loss of expression of the CDK2NA via either methylation or loss of chromosome 9p is associated with malignant progression of low grade gliomas.

Proliferative Index and Recurrence

Level III. It is recommended that proliferative indices (MIB-1 or BUdR) be measured in low grade gliomas as higher proliferation indices are associated with increased likelihood of recurrence and shorter progression-free and overall survival.

1p/19q Status and Recurrence

There is insufficient evidence to make any recommendations.

Chemotherapy at Recurrence

Question

What role does chemotherapy have in low grade glioma recurrence?

Recommendations

Temozolomide and Recurrence

Level III. Temozolomide is recommended in the therapy of recurrent low grade glioma as it may improve clinical symptoms. Oligodendrogliomas and tumors with 1p/19q co-deletion may derive the most benefit.

Procarbazine, Lomustine, Vincristine (PCV) and Recurrence

Level III. PCV is recommended in the therapy of low grade glioma at recurrence as it may improve clinical symptoms with the strongest evidence being for oligodendrogliomas.

Carboplatin and Recurrence

Level III. Carboplatin is not recommended as there is no significant benefit from carboplatin as single agent therapy for recurrent low grade gliomas.

Other Treatments (Nitrosureas, Hydroxyurea/Imatinib, Irinotecan, Paclitaxel) and Recurrence

There is insufficient evidence to make any recommendations. It is recommended that individuals with recurrent low grade gliomas be enrolled in a properly designed clinical trial to assess these chemotherapeutic agents.

Radiation at Recurrence

Question

What role does radiation have in low grade glioma recurrence?

Recommendations

Radiation at Recurrence with No Previous Irradiation

Level III. Radiation is recommended at recurrence if there was no previous radiation treatment.

Re-irradiation at Recurrence

Level III. It is recommended that re-irradiation be considered in the setting of low grade glioma recurrence as it may provide benefit in disease control.

Surgery at Recurrence

There is insufficient evidence to make any specific recommendations. It is recommended that individuals with recurrent low grade gliomas be enrolled in a properly designed clinical trial to assess the role of surgery at recurrence.

Definitions

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Evidence on Therapeutic Effectiveness and Levels of Recommendation

Evidence Classification	
Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g., case control and cohort studies)
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls
Levels of Recommendation	
Level 1	Generally accepted principles for patient management, which reflect a high degree of clinical certainty (usually this requires Class I evidence which directly addresses the clinical questions or overwhelming Class II evidence when circumstances preclude randomized clinical trials)
Level 2	Recommendations for patient management which reflect clinical certainty (usually this requires Class II evidence or a strong consensus of class III evidence)
Level 3	Other strategies for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion)

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Recurrence of diffuse low grade glioma

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Neurological Surgery

Neurology

Oncology

Pathology

Radiation Oncology

Radiology

Intended Users

Physicians

Guideline Objective(s)

To systematically review the literature for the management of recurrent low grade gliomas

Target Population

Adult patients with recurrent low grade glioma with initial pathologic diagnosis of a World Health Organization (WHO) grade II infiltrative glioma (oligodendroglioma, astrocytoma, or oligo-astrocytoma)

Interventions and Practices Considered

Evaluation

1. Determination of isocitrate dehydrogenase (IDH) mutation status
2. Assessment of methylguanine methyltransferase (MGMT) status
3. Assessment of CDK2NA status
4. Measurement of proliferative indices (MIB-1 or BUdR)

Management/Treatment

1. Temozolomide (TMZ)
2. Procarbazine, lomustine, vincristine (PCV)
3. Radiation therapy
4. Re-irradiation at recurrence

Note: The following were considered but not recommended: determination of TP53 status; carboplatin; nitrosureas, hydroxyurea/imatinib, irinotecan, and paclitaxel; surgery at recurrence. There was insufficient evidence to make a recommendation for or against determination of Ip/I9q status.

Major Outcomes Considered

- Recurrence rate
- Survival rate (progression-free and overall)
- Post-recurrence survival rate
- Response rate
- Time to recurrence
- Prognostic value of pathologic and molecular characteristics in the prediction of outcome/malignant transformation at recurrence

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

General Search Strategy

Literature Examination Approach

A wide-ranging literature search strategy was undertaken to identify all citations relevant to the management of low grade gliomas (LGGs). The MEDLINE and EMBASE electronic databases were searched from 1990 through 2012, with additional data being gleaned from the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Registry, and Cochrane Database of Abstracts of Reviews of Effects. The search strategies used a combination of subheadings and text words with the specifics of this work being outlined in each guideline section. Reference lists of the publications chosen for full text review were also screened for potentially relevant studies.

Study Selection

The search of the bibliographic databases identified possibly relevant citations for a given topic and often these were large in number. The eligibility (inclusion/exclusion) criteria to screen the citations for each of the questions were determined ahead of time for each section by the writing group. At least two authors evaluated the titles and abstracts using the inclusion and exclusion criteria with broad interpretation of the criteria being used initially so as to maximize the likelihood of capturing pertinent information. Cases of disagreement about pertinence were resolved by a third author when needed. The full text articles of the selected abstracts were then collected and the same process of applying the eligibility criteria was carried out again with the more in depth information available. Articles that met the eligibility criteria were grouped according to the questions they addressed and used to create the evidence tables and scientific foundation sections. Reasons for exclusion for papers were also documented so as to be able to discuss pertinent problem citations in the scientific foundation as needed.

Specific Search Strategy for This Guideline

Literature Review

The following electronic databases were searched from 1990 to December 2012: PubMed and Cochrane Database of Systematic Reviews using relevant MeSH and non-MeSH terms, including "glioma", "low grade glioma", "recurrence", "neoplasm recurrence, local", "disease progression", "astrocytoma", and "low grade astrocytoma."

Article Inclusion and Exclusion Criteria

Eligibility Criteria

- Peer-reviewed publications
- Patients with recurrent World Health Organization (WHO) grade II oligodendroglioma, astrocytoma, or oligo-astrocytoma or imaging suggestive of those diagnoses. In publications with mixed populations, those patients with recurrent diagnosed WHO grade II tumor were included if their information could be isolated and analyzed separately from the remainder of the reported cohort.
- Each study had at least five or more study participants with previously confirmed WHO grade 2 tumors suspicious for recurrence
- Patients greater than 17 years of age. Studies with mixed adult and child populations were included if the adult cohorts could be isolated and analyzed separately.
- Publications in English

Study Selection

The search criteria was examined and performed by two independent reviewers. Citations were independently reviewed and included if they met the a priori criteria for relevance. No discrepancies in study eligibility were noted. Corresponding full-text PDFs were obtained for all citations meeting the criteria, and reviewed.

Number of Source Documents

Overall, 617 studies met the eligibility criteria and were screened for inclusion. Of these, 54 studies met the criteria and specifically focused on the management of recurrent low-grade gliomas in adult patients. Figure 1 in the original guideline document depicts the number of studies in each part of the selection and review process.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Evidence on Therapeutic Effectiveness

Evidence Classification	
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Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g., case control and cohort studies)
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

General Evidence Analysis

Quality Assessment and Statistical Analysis

Articles that met the eligibility criteria were grouped according to the questions they addressed and used to create the evidence tables and scientific foundation sections. Reasons for exclusion for papers were also documented so as to be able to discuss pertinent problem citations in the scientific foundation as needed.

Studies which met the eligibility criteria were subject to more detailed scrutiny and had their data extracted by one reviewer and the extracted information was checked by one or more other reviewers. Evidence and summary tables, reporting the extracted study information and evidence classification, were generated for all of the included studies for each of the questions. Evidence tables were created with most recent data first and subsequent listings in retrograde chronological order. The table headings consisted of first author name and year, followed by a brief study description, chosen data class and conclusion. The authors were directed to craft the data in the tables in a succinct and fact filled manner so as to allow for understanding of the literature entry. The literature in the evidence tables was expanded upon in the scientific foundation of each section so as to emphasize important points supporting its classification and contribution to recommendations. The method by which this was accomplished is expanded upon in the Joint Guideline Committee Guideline Development Methodology document (see the "Availability of Companion Documents" field). Internal drafts of the tables and manuscripts were developed by sharing between writers electronically, by telephone and meetings. Summary and conclusion statements were included for each section, with comments on key issues for future investigation being added where pertinent.

Specific Evidence Analysis for This Guideline

Quality Assessment

Data was extracted by the first reviewer and verified by the other, all of which were compiled into evidence tables corresponding to Pathology,

Surgery, Chemotherapy, and Radiation Therapy. The tables and data were reviewed by all of the authors.

Evidence Classification and Recommendation Levels

Each reviewer independently determined the strength of the evidence, classified it according to the criteria described in the "Rating Scheme for the Strength of the Evidence" field, and a consensus level of recommendation was achieved.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Panel Development

Recognizing the serious nature of low grade gliomas along with the lack of consensus among various treatment options, the Joint Tumor Section of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) recommended that evidence-based guidelines be developed as a top priority, for the diagnosis, management and treatment of low grade glioma patients. The objectives of these guidelines are to establish the best evidence-based management of low grade gliomas in terms of imaging diagnosis, use of surgical biopsy and resection, assessment of tumor pathology, administration of systemic chemotherapy, and administration of radiation therapy. Because these tumors dependably recur or progress despite standard therapy, the Joint Tumor Section also recommended an evidence-based guideline be developed for progressive low grade gliomas and that information on promising emerging therapies be assessed in the same manner to determine the possible application of these findings.

Having identified the topical objectives, the Guidelines Committee of the Joint Tumor Section then recruited experts in the field from each of the parent organizations as lead writers of each section. These writers, in turn, recruited experts in non-neurosurgical specialties relevant to the field of management and therapy chosen. Writers were provided training on the method of guideline development as used in this guideline set by written methods and instructions. The senior authors and CNS Guidelines Manager then worked with them on a step by step basis to confirm that the methods were followed as the literature was collected, assessed and documents developed. When writers were approached and preliminarily agreed to participate they were asked to complete a formal conflict of interest questionnaire confirming the appropriateness of their participation. At that point they also agreed to report any new conflicts of interest that might develop during the writing process. In this manner a multidisciplinary panel of writers referred to as the Low Grade Glioma Guidelines Task Force was assembled, with significant administrative, logistical and analytical support from the national CNS Guidelines Committee. The method of this evidence-based clinical practice parameter guideline has been written in a manner to be as transparent as possible using published assessment criteria.

Topic Range of This Systematic Review and Clinical Practice Guideline

Having identified writing groups for each topic, the members designed questions to allow assessment of the literature in a manner that would provide guidance for management of low grade gliomas. These questions are presented at the beginning of each of the eight guideline chapters spanning the topics of imaging assessment, diagnostic biopsy, surgical resection, tumor evaluation by standard neuropathology and molecular techniques, radiation therapy, chemotherapy, emerging therapies and treatment of recurrent or progressive low grade gliomas.

Guideline Panel Consensus

Multidisciplinary writing groups were created for each section based on author expertise, in order to address each of the disciplines and particular areas of therapy selected for these clinical guidelines. Each group was involved with literature selection, creation and editing of the evidence tables and scientific foundations for their specific section and discipline. Using this information, the writing groups then drafted the recommendations in answer to the questions formulated at the beginning of the process, culminating in the clinical practice guideline for their respective discipline. The draft guidelines were then circulated to the entire clinical guideline panel to allow for multidisciplinary feedback, discussion, and ultimately approval.

Rating Scheme for the Strength of the Recommendations

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Levels of Recommendation

Levels of Recommendation	

Levels of Recommendation	
Level 1	Generally accepted principles for patient management, which reflect a high degree of clinical certainty (usually this requires Class I evidence which directly addresses the clinical questions or overwhelming Class II evidence when circumstances preclude randomized clinical trials)
Level 2	Recommendations for patient management which reflect clinical certainty (usually this requires Class II evidence or a strong consensus of class III evidence)
Level 3	Other strategies for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion)

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Approval Process

The completed evidence-based clinical practice guidelines for the management of low grade gliomas were presented to the Joint Guidelines Committee of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) for review. The reviewers for the Joint Guidelines Committee were vetted by the *Journal of Neuro-oncology* for suitability and expertise to serve as reviewers for the purposes of publication in that journal also. The final product was then approved and endorsed by the executive committees of both the AANS and CNS prior to publication in the *Journal of Neuro-oncology*.

The funding agencies (CNS Executive Committee and AANS/CNS Joint Tumor Section Executive Committee) were permitted to review these guidelines only after the Joint Guidelines Committee had completed its extensive review, critique and ultimate approval process; the funding groups then were limited to whether or not to endorse or reject this body of work but substantive changes were not allowed.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The role of surgery in recurrence, at current, is to provide symptomatic relief and improved diagnosis as nothing in the literature meets criteria to address progression and overall survival benefit. Chemotherapeutic options at recurrence are varied and investigation comparing the benefits of different agents has yet to be studied in a prospective manner. Retrospective evidence appears to suggest an effective response rate and relatively beneficial outcomes in uncontrolled studies of temozolomide (TMZ) and procarbazine, lomustine, vincristine (PCV); however, further investigation is needed. Similarly, radiation therapy at recurrence appears to have survival benefit specifically in the radiation naïve patient; however, future prospective investigations are necessary.

Refer to the evidence tables in the original guideline document for further discussion of benefits found in specific studies.

Potential Harms

Toxicity of chemotherapy and radiotherapy (refer to the evidence tables in the original guideline document for toxicities reported in specific studies)

Qualifying Statements

Qualifying Statements

The information in these guidelines reflects the current state of knowledge at the time of completion. Each section is designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Nahed BV, Redjal N, Brat DJ, Chi AS, Oh K, Batchelor TT, Ryken TC, Kalkanis SN, Olson JJ. Management of patients with recurrence of diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2015 Dec;125(3):609-30. [56 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Dec

Guideline Developer(s)

American Association of Neurological Surgeons - Medical Specialty Society

Congress of Neurological Surgeons - Professional Association

Source(s) of Funding

These guidelines were funded exclusively by the Congress of Neurological Surgeons (CNS) Guidelines Committee, with no funding from any outside commercial sources. Development of this set of evidence-based clinical practice guidelines was editorially independent from the funding agencies.

Guideline Committee

American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee

Low Grade Glioma Guidelines Task Force

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Conflict of Interest

Low Grade Glioma Guidelines Task Force members were required to report all possible conflicts of interest (COIs) prior to beginning work on the guideline, using the COI disclosure form of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of Task Force Members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs.

Disclosures

Dr. Batchelor is a consultant for EMD-Serono. Dr. Kalkanis is a consultant for Arbor and Varian. Dr. Olson is a consultant for the American Cancer Society; has received research funding from the National Cancer Institute, Genentech, and Millennium; and has received investigational drug provision from Merck.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Journal of Neuro-Oncology Web site .

Availability of Companion Documents

The following are available:

- Rock J. Low grade glioma guidelines: foreword. J Neurooncol. 2015 Dec;125(3):447-8. Available from the Journal of Neuro-Oncology Web site .
- Olson JJ, Kalkanis SN, Ryken TC. Evidence-based clinical practice parameter guidelines for the treatment of adults with diffuse low grade glioma: introduction and methods. J Neurooncol. 2015 Dec;125(3):449-56. Available from the Journal of Neuro-Oncology Web site .
- Congress of Neurological Surgeons (CNS). Guideline development methodology: endorsed by the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the AANS/CNS Joint Guideline Committee. Schaumburg (IL): Congress of Neurological Surgeons (CNS); 2012 Feb. 12 p. [2 references]. Available from the Congress of Neurological Surgeons Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 7, 2016. The information was not verified by the guideline developer.

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